UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

005634

DEC 15 1986

MEMORANDUM

Subject: Dr. Swenberg's Evaluation of the Brain Slides for the 2,4-Dichlorophenoxyacetic acid Rat Study

To: Lynn Vlier
Special Review,
Registration Division TS-767C

From: Marcia van Gemert, Ph.D. Marcia van Gemert 12.11.86
Head, Section III
Toxicology Branch, HED

Thru: Theodore M. Farber, Ph.D. Theodore M. Farber 12/15/86
Chief, Toxicology Branch, HED

Chemical: 2,4-Dichlorophenoxyacetic acid

Tox Chem #: 315

Project No: None

Dr. Swenberg met with Dr. Theodore Farber and myself on November 19, 1986 and conveyed both the box of brain slides and his histopathological diagnoses of these slides to us.

For all but one animal, he agreed with the original study text diagnoses of astrocytomas. He disagreed with the astrocytoma diagnosis of female B23289 in the 5 mg/kg group. He diagnosed this lesion as a focal area of gliosis present near the center of the olfactory bulb, no neoplasm was detected. The study text however had diagnosed this area as an astrocytoma. He also disagreed with Dr. Koestner's diagnosis of the male B23473 of the 45 mg/kg group. Dr. Koestner had diagnosed the brain section in question of this animal as consisting of a mixed glial and mesenchymal cell population. Dr. Swenberg diagnosed this animal as having a small astrocytoma present in the ventral portion of one hemisphere of the forebrain.

Dr. Swenberg was asked if he felt this study provided sufficient evidence to classify 2,4-D an oncogen. He said the data were very equivocal for a number of reasons. Astrocytomas are not as uncommon as previously thought. These tumors are very small as a general rule, and more vigorous examination and sectioning tend to increase the numbers found. He had seen a similar circumstance when examining the slides from a rat study on Harvade. At that time he suggested that another study be performed to resolve the equivocal astrocytoma

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issue. This study should include a larger group size, two control and one high dose group, looking at brain sections only at termination of the experiment. He stated that this was his recommendation also for 2,4-D in order to attempt to resolve this astrocytoma issue.

Appended page 1 contains the original table of tumor incidences from the study text, and appended page 2 presents Dr. Swenberg's diagnoses in tabular form by animal number. Appended pages 3 and 4 present the study text's original diagnoses and appended pages 5 and 6 present Dr. Swenberg's diagnoses.

Appendix 13-1

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"Contains or relates to trade secrets confidential or proprietary informatio of the industry task force on 2, 4-D research data."

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Text Table 1
Incidence of astrocytomas in the brain of F-344 rats receiving 2,4-Dichlorophenoxyacetic acid at 0, 1, 5, 15, or 45 mg/kg/day

		Male					Female				
	Group:	1	2	3	4	5	1	2	3	4	5
Mg/Kg/Day	2,4-D:	0	1	5	15	45	0	1	5	15	45
Unscheduled Deaths:		1/18	0/7	0/3	2/7	1/14	0/10	1/13	0/13	0/12	0/14
Post Week 52 Interim Sacrifice:		0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Post Week 104/105 Terminal Sac.		0/32	0/43	0/47	0/41	5/36	0/40	0/37	2/37	1/38	1/36
All Animals on Study:		1/60	0/60	0/60	2/58	6/60	0/60	1/60	2/60	1/60	1/60

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Astrocytoma Incidence as Diagnosed by Dr. Swenberg

Males:

Dose:	0 mg/kg	1 mg/kg	5 mg/kg	15 mg/kg	45 mg/kg
Animal #	B23025			B23376 B23377	B23473 B23476 B23479 B23492 B23500 B23505

Females:

Animal #		B23185	B23302	B23442	B23546

Characteristics of Primary Brain Neoplasms in F344 Rats on a Two-Year 2,4 - Dichlorophenoxyacetic Acid Feeding Study

Group	Dose mg/kg/day	Animal Number	Sex	Diagnosis	Location[1]	Size[2]	Pattern of Infiltration[3]	Cellular Pleomorphism	Other Features
				Terminal (104/105 Week) Sacrifice					
1	0	23024	M	Granular Cell Tumor	M,C(midline)	S	C	minimal	Nodular and compressive. Cells with eosinophilic cytoplasmic granules. No mitoses.
5	45	23473*	M	Astrocytoma	C(t)	M	Pc	slight	Small round, oval to spindle nuclei, perivascular cuffing. No mitoses.
5	45	23476	M	Astrocytoma	Cb,M	L	D	slight	Small round to oval nuclei, cavitation, hemosiderin. No mitoses.
5	45	23479	M	Astrocytoma	C(t)	M	Pc	slight	Small round to oval nuclei, perivascular cuffing. No mitoses.
5	45	23492	M	Astrocytoma	C(p,t),M	L	D	slight	Small round to oval nuclei, hemosiderin. Moderate mitoses.
5	45	23500	M	Astrocytoma	C(f)	L	D	minimal	Small round nuclei, perivascular cuffing. Few mitoses.
3	5	23289*	F	Astrocytoma	Cb	S	Pc	minimal	Oval to spindle nuclei. No mitoses.
3	5	23302	F	Astrocytoma	C(t)	S	Pc	minimal	Small round to oval nuclei. Minimal mitoses.
4	15	23442	F	Astrocytoma	C(f,p)	L	D	minimal	Small round to oval nuclei, perivascular cuffing, minimal necrosis and hemosiderin. No mitoses.
5	45	23546	F	Astrocytoma	C(midline)	L	D	slight	Small round to spindle nuclei, perivascular cuffing. Many mitoses.

[1] C = Cerebrum (f = frontal, p = parietal, t = temporal, o = occipital); Cb = Cerebellum; H = Hippocampus, M = Meninges; Bs = Brain stem; Ob = Olfactory bulb.
[2] S (small) = <2mm; M (medium) = 2 - 4mm; L (large) = > 4mm.
[3] C = Circumscribed; Pc = Poorly circumscribed; D = Diffuse.
* Tumors found in newly embedded brain tissue but not present in originally embedded brain tissue.

Characteristics of Primary Brain Neoplasms in F344 Rats on a Two-Year 2,4 - Dichlorophenoxyacetic Acid Feeding Study

Group	Dose mg/kg/day	Animal Number	Sex	Diagnosis	Location[1]	Size[2]	Pattern of Infiltration[3]	Cellular Pleomorphism	Other Features
				Found Dead and Moribund Sacrifice					
1	0	23025	M	Astrocytoma	C(t,p,o),M	L	D	minimal	Small round nuclei, necrosis, cavitation, hemorrhage, perivascular cuffing. Few mitoses.
4	15	23376	M	Astrocytoma	C(o)	M	Pc	minimal	Small round to oval nuclei, perivascular cuffing. No mitoses.
4	15	23377	M	Astrocytoma	C(f,p,t) (bilateral)	L	D	slight	Small round to oval nuclei, necrosis, hemosiderin, perivascular cuffing, meningeal infiltration. Minimal mitoses.
5	45	23505*	M	Astrocytoma	Ob	S	Pc	slight	Small round to spindle nuclei, perivascular cuffing, meningeal infiltration. Minimal mitoses.
2	1	23185	F	Astrocytoma	Bs	M	Pc	minimal	Small round to oval nuclei, perivascular cuffing. No mitoses.

[1] C = Cerebrum (f = frontal, p = parietal, t = temporal, o = occipital); Cb = Cerebellum; H = Hippocampus, M = Meninges; Bs = Brain stem; Ob = Olfactory bulb.
[2] S (small) = <2mm; M (medium) = 2 - 4mm; L (large) = > 4mm.
[3] C = Circumscribed; Pc = Poorly circumscribed; D = Diffuse.
* Tumors found in newly embedded brain tissue but not present in originally embedded brain tissue.

Histopathologic Examination of Brain Sections from Study 2184-103

Animal Number			Number of Slides	Histopathologic Findings
0 mg/kg/day	B23024	M	2	A small granular cell tumor is present in the cerebellar meninges that has invaded into the dorsal cerebellum.
0 mg/kg/day	B23025	M	2	A large cystic mixed glioma extends from the forebrain to the occipital lobe of one cerebral hemisphere.
1 mg/kg/day	B23185	F	3	A microscopic astrocytoma is present in the ventral medulla.
5 mg/kg/day	B23289	F	2	A focal area of gliosis is present near the center of the olfactory bulb. No neoplasm was detected.
5 mg/kg/day	B23302	F	3	The ventral forebrain contains an area of increased cellularity. This lesion is present in only one section but appears compatible with a microscopic astrocytoma.
15 mg/kg/day	B23376	M	5	There is an area of focal gliosis/early tumor present in the dorsal forebrain. In addition, the most anterior portion of the forebrain adjacent to the olfactory bulb has meningeal filtration of mononuclear cells having a similar astrocytic morphology. Diagnosis: Microscopic astrocytoma.
15 mg/kg/day	B23377	M	3	A large diffuse astrocytoma extends from the frontal region of the brain to the occipital lobe of the brain.
15 mg/kg/day	B23442	F	2	A small to moderate sized diffusely invading astrocytoma is present in one hemisphere of the forebrain.
45 mg/kg/day	B23473	M	3	A small astrocytoma is present in the ventral portion of one hemisphere of the forebrain.
45 mg/kg/day	B23476	M	2	The cerebellum contains an astrocytoma.
45 mg/kg/day	B23479	M	2	A small astrocytoma is present in the striatum of one hemisphere of the forebrain.

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Histopathologic Examination of Brain Sections from Study 2184-103 (cont'd)

Animal Number		Number of Slides	Histopathologic Findings
45mg/kg/day	B22492 M	3	One hemisphere of the cerebellum contains a diffusely invading astrocytoma.
45mg/kg/day	B23500 M	2	A diffusely invasive astrocytoma extends from the forebrain to the thalamus.
45mg/kg/day	B23505 M	2	A small astrocytoma is present in the olfactory bulb of the brain.
45mg/kg/day	B23546 F	2	The brain contains an astrocytoma extending from the thalamus to the midbrain with secondary hydrocephalus.

11/19/86

END